

REMARKS

This Amendment corrects a typographical error in claim 51. No new matter has been added. Claims 51-58 are pending.

Examiner Wheeler is thanked for noting the typographical error in claim 51, which has been corrected in accordance with the Examiner's helpful suggestion. Reconsideration and withdrawal of the objection to claim 51 are requested.

The 35 U.S.C. § 103(a) rejection of claims 51-58 over the Kortesuso Dissertation (2001) in view of Kortesuso et al., 76 J. Controlled Release 227 (2001) is traversed. The claimed bioresorbable sol-gel derived SiO₂ is prepared by a specified process and has a very fast dissolution rate (at least 2.0 wt-%/hour for monoliths, at least 0.15 wt-%/hour for coatings and at least 1.0 wt-%/hour for particles). See claims 51 and 58. Alternatively, the claimed bioresorbable sol-gel derived SiO₂ has a slow dissolution rate (0.001 to 0.05 wt-%/hour) for monoliths or coatings. See claim 55. The inventors have discovered a very fast *in vitro* dissolution rate can be achieved using a combination of specified precursor ratios (e.g., a water to alkoxide ratio of 0.5 to 2.5, and alcohol to alkoxide ratio of at least 0.5), and an initial sol pH of 0.05 to 2.5. A slower dissolution rate can be

achieved by departing from these specified sol-gel processing parameters.

The cited combination of references fails to raise a *prima facie* case of obviousness against the claimed sol-gel derived SiO₂. Neither the Kortesus Dissertation nor Kortesus et al. disclose or suggest a sol-gel derived SiO₂ monolith having an *in vitro* dissolution rate of at least 2.0 wt-%/hour, or the specific combination of precursor ratios, pH and drying conditions necessary to produce such an unexpectedly fast dissolving SiO₂ monolith. The following points are made in response to the arguments contained in the Official Action:

1. Product-by-process Claims - Applicants agree their claims are product-by-process claims, and that their patentability depends on product features, such as their very fast (claims 51-54 and 58) or slow (claims 55-57) *in vitro* dissolution rates.
2. The Kortesus Dissertation Fails to Disclose the Claimed SiO₂ Monoliths - The Kortesus Dissertation does not disclose monoliths having an *in vitro* dissolution rate of at least 2.0 wt-%/hour. Similarly, the Kortesus Dissertation does not disclose monoliths having an *in*

vitro dissolution rate of from 0.001 to 0.05 wt-%/hour.¹

Moreover, and as explained in detail below, one of ordinary skill in the art could not arrive at the claimed SiO₂ monoliths, coating and particles from the combined disclosures of the Kortesus Declaration and Kortesus et al.

3. Applicants' Starting Point Ranges Are Critical - The claimed bioresorbable SiO₂ is prepared using a sol-gel process. Independent claims 51, 55 and 58 each require the starting conditions in a sol comprising water, an alkoxide and a lower alcohol to be as follows:
- i) pH is from 0.05 to 2.5,
 - ii) molar ratio of water to the alkoxide or inorganic silicate is 0.5 to 2.5,
 - iii) molar ratio of alcohol to the alkoxide or inorganic silicate is ≥ 0.5 .

¹The Patent Office argument that the Kortesus Dissertation teaches monolith degradation times as long as 4 months (Official Action, page 6, second paragraph) is incorrect because the cited disclosure (page 35, 6.1.3) relates to alkyl-substituted monoliths (25 mol% substitution with DMDES). In contrast, the claimed sol-gel derived SiO₂ has no such substitution. See the definition of *sol-gel derived SiO₂* on page 11, lines 13 to 24, of the application.

The inventors have discovered that starting the sol-gel process with a sol having these specific properties enables production of SiO₂ monoliths, coatings and particles having unexpectedly fast *in vitro* dissolution rates. Moreover, they have discovered what process changes produce SiO₂ monoliths, coatings and particles having slower dissolution rates (Specification, pages 18-22).

In contrast, the cited prior art fails to disclose this combination of sol starting conditions, and also fails to disclose or suggest the importance of either (i) permitting condensation and/or aggregation to proceed freely or (ii) preventing condensation and/or aggregation by forced gelling. In short, one of ordinary skill in the art cannot arrive at the claimed SiO₂ monoliths, coatings and particles from the teachings of the Kortesuso Dissertation and Kortesuso et al.

4. Those of Ordinary Skill Cannot Arrive at the Claimed SiO₂ by "Routine Optimization" - Page 7, lines 17-22, of the Official Action contain the following, *demonstrably erroneous*, argument:

It would have been obvious to one of ordinary skill in the art at the time to provide a sol-gel derived SiO₂ monolith having desired biodegradability by optimizing the surface area (particle diameter), porosity, pH and the water/alkoxide ratio by following the guidance provided from the teachings of Kortesuso.

There are at least two reasons why this "routine optimization" argument is incorrect. First, the polymerization of SiO_2 is very complex and different² from that of carbon-based compounds. The complexity of SiO_2 polymerization explains the great variety in the properties of the obtained polymers, and the difficulty confronting those of ordinary skill who attempt to produce SiO_2 products with specific properties such as a specific *in vitro* dissolution rate.

Second, the Kortesus Dissertation discussion of specific factors demonstrates they cannot be "routinely optimized" to achieve the claimed SiO_2 monolith having an *in vitro* dissolution rate of at least 2.0 wt-%/hour:

A. "Optimizing" Surface Area

The Kortesus Dissertation teaches the porosity/surface area and geometry of the sol-gel derived SiO_2 affects its degradation rate. See page 31 ("In general, the porous structure of cast silica xerogel monoliths resulted in a faster...degradation of the matrix as compared to spray-dried particles.") Table 4 (page 32) of the Kortesus Declaration teaches that a monolith having a specific surface area of approximately 400 m^2 will have a faster

²The chemical structure of SiO_2 is more complex than suggested by its formula. See the attached exhibit, which shows how the polymerization of SiO_2 can occur via at least 2 different levels and most probably 3 levels.

overall degradation time (days to months) than microparticles having a specific surface area of less than 10 m^2 (days to more than a year). Yet other properties are often more important to SiO_2 degradation rate than surface area, as demonstrated by Fig. 2 of Viitala et al., "Adjustably Bioresorbable Sol-Gel Derived SiO_2 for Release of Large Biologically Active Molecules", 36 J. Sol-Gel Sci. & Tech. 147 (2005) which shows that despite a much smaller specific surface area (3.4), the degradation rate of monolith Bm12 is clearly faster than that of monoliths Bm11 (ssa of 43), Am03 (ssa of 637) and AM01 (ssa of 697).

Accordingly, one of ordinary skill in the art could not "routinely optimize" the SiO_2 dissolution rate by simply reducing the specific surface area of the monolith.

B. "Optimizing" pH

Table 4 (page 32) of the Kortesus Dissertation states the "optimum synthesis pH for both monoliths and microparticles is between pH 2-3, presumably because the optimum release profile for dexmedetomidine is stated to be obtained at this pH. Table 2 (page 28) lists silica gel monolith dissolution percentages exhibited by monoliths prepared from sols having a pH of 1, 2.3, 3 and 5. However, the data does not appear to show any trend. More

particularly, the dissolution percentages for monoliths prepared with the water/TEOS ratio held constant at 14 do not appear to vary *as a function of pH*:

<u>pH</u>	<u>R</u>	<u>Silica Dissolution %</u>
1	14	25.5
2.3	14	16.9
3	14	25.7
5	14	21.7

While the silica dissolution rate obviously varies, one of ordinary skill would not interpret this data to suggest that simply increasing or reducing pH will necessarily increase or reduce the silica dissolution rate. Increasing the pH from 1 to 2.3 reduced the monolith's silica dissolution rate. Yet further increasing pH from 2.3 to 3 increased the silica dissolution rate to 25.7, even higher than exhibited by monoliths prepared from sols having a pH of 1. However, further increasing pH from 3 to 5 again reduced the monolith dissolution rate.

Accordingly, one of ordinary skill in the art could not "routinely optimize" the starting sol pH according to the disclosure of the Kortessuo Dissertation in order to arrive at a desired silica monolith dissolution rate.

C. "Optimizing" the water/alkoxide ratio

Table 2 (page 28) of the Kortesus Declaration also lists silica gel monolith dissolution percentages exhibited by monoliths prepared from sols having a pH of 2.3, but whose water/TEOS ratio ("R") were varied:

<u>pH</u>	<u>R</u>	<u>Silica Dissolution %</u>
2.3	6	17.8
2.3	14	16.9
2.3	28	20.4

First, the data does not appear to show any trend. Raising the R ratio from 6 to 14 reduces the silica dissolution ratio, while raising the R ratio again increases the silica dissolution rate. Second, the actual change in dissolution rate is rather small: the SiO₂ degradation rate range of 16.9 to 20.4%/30 h is only 0.56 to 0.68 wt-%/h over a rather wide R range of 6 to 28. The degradation rate for microparticles (also listed in Table 2) is broader, but even here the degradation rate is limited to 0.01 to 0.67 wt-%/h despite using a broader R ratio range of 6 to 35.

Accordingly, one of ordinary skill in the art could not "routinely optimize" the water/alkoxide ratio according to the

**disclosure of the Kortesus Dissertation in order to arrive at a
desired silica monolith dissolution rate.**

* * * * *

Page 35, lines 33-36, of the Kortesus Dissertation suggest the degradation rate of the silica xerogel can be "modified" by "varying" the composition of the starting materials, or by varying the manufacturing method from casting to spray drying. Yet the data in the Kortesus Dissertation demonstrates this statement is merely an invitation to experiment, rather than guidance to one of ordinary skill in the art seeking to prepare a sol-gel derived SiO₂ monolith, coating or particle having a very fast dissolution rate.

The Kortesus Dissertation demonstrates the prior art did not understand which factors are decisive to control the dissolution rate of bioresorbable sol-gel derived SiO₂. It provides one of ordinary skill only a very limited ability to adjust the dissolution rate of a sol-gel derived silica monolith.

In short, the Kortesus Dissertation fails to disclose or suggest a starting point for correlating the values necessary to produce a sol-gel derived SiO₂ having a specific dissolution rate, as demonstrated by the results listed in its Table 2. In stark contrast, the present application provides such a starting point.

The application defines what changes result in slower dissolution rates, and defines the provisos related to having these changes reduce the dissolution rate. See pages 18 to 22 of the application.

The present invention offers those of ordinary skill in the art great versatility in the production of a bioresorbable sol-gel derived SiO_2 , i.e., the ability to obtain a desired *in vitro* dissolution rate over a great dissolution range and with certainty. These advantages were unforeseen from the Kortesuso Dissertation and the other prior art of record.

Kortesuso et al. does not provide any additional information which would permit one of ordinary skill in the art to arrive at the claimed sol-gel derived SiO_2 . Reconsideration and withdrawal of the obviousness rejection of claims 51-58 are respectfully requested.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of the obviousness rejection of claims 51-58, and issuance of a Notice of Allowance directed to those claims, are earnestly requested. The Examiner is urged to telephone the undersigned should he believe any further action is required for allowance.

U.S. Patent Appln. S.N. 10/590,451
AMENDMENT

PATENT

It is not believed any fee is required for entry and consideration of this Amendment. Nevertheless, the Commissioner is authorized to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

/James C. Lydon/

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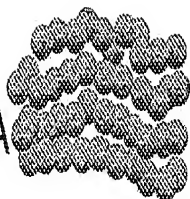
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Enclosures:
Petition for Extension of Time
Appendix

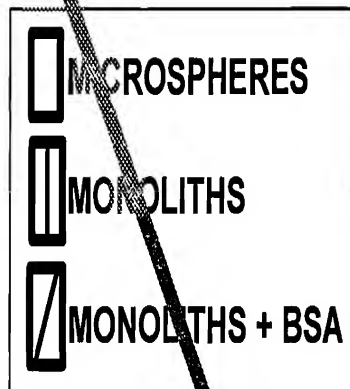
NMR	Q ₂ %	Q ₃ %	Q ₄ %	Q ₄ /(Q ₂ +Q ₃)
Am-monolith	18,4	27,6	54,0	1,17
Bs-Microsph	0	79,6	20,4	0,26

← Degree of Condensation

Denser,
Low SSA

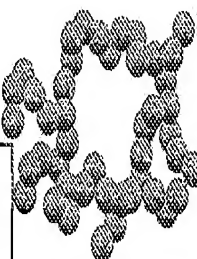


Bs15: SSA = 4,3

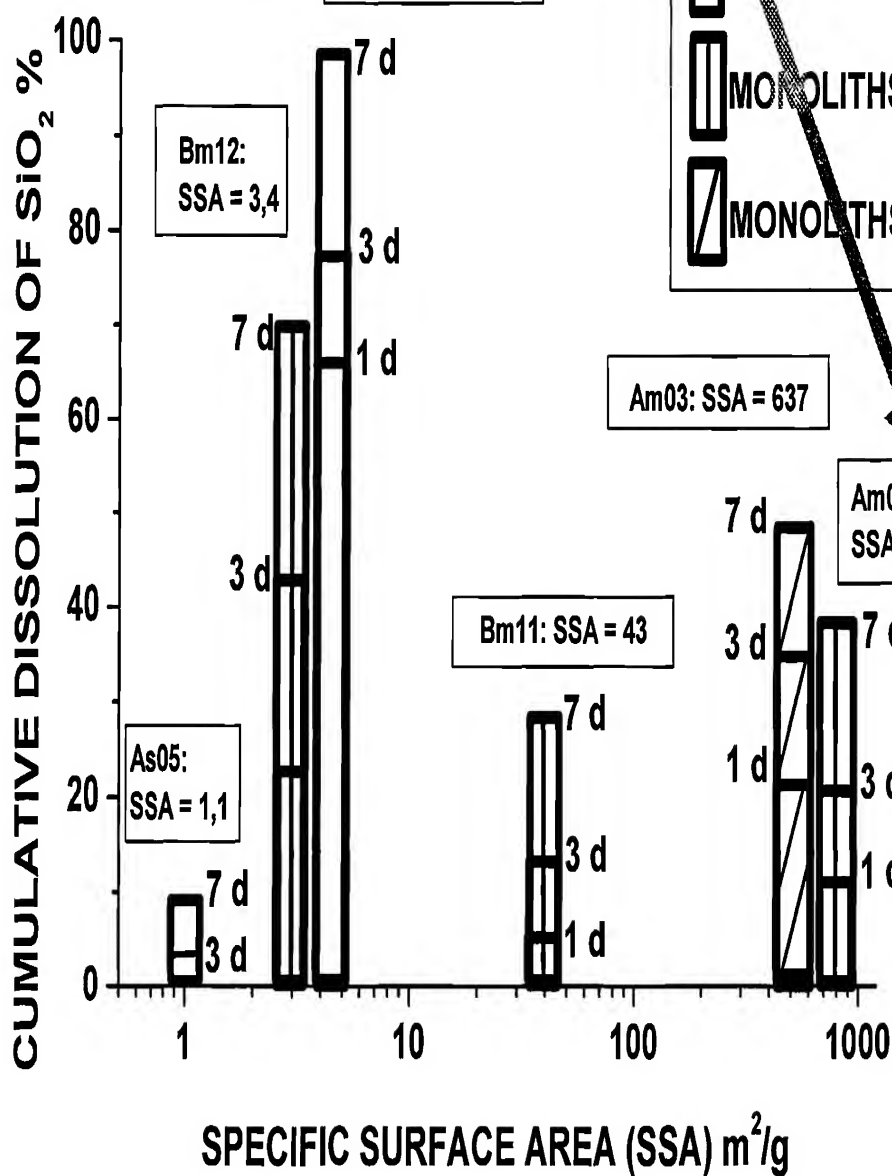


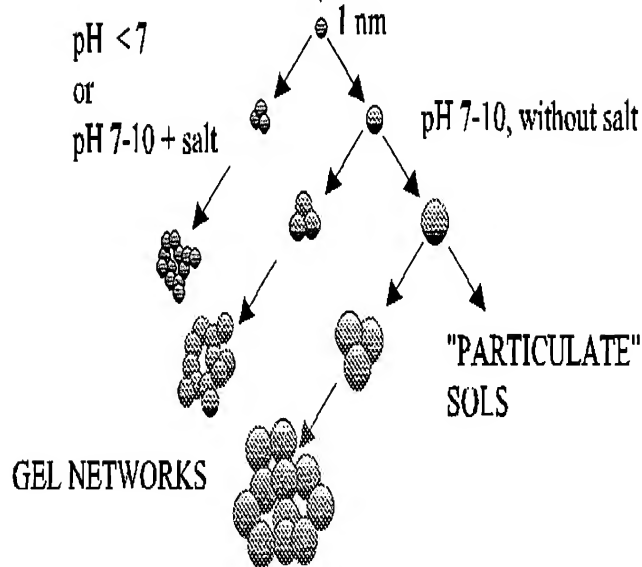
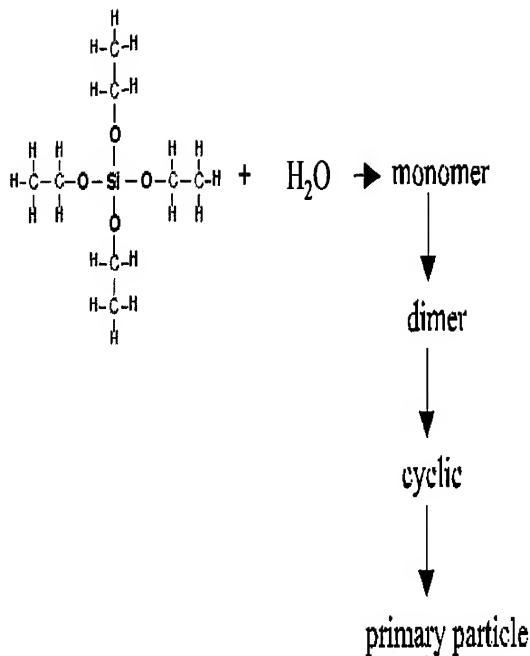
Am03: SSA = 637

Am01:
SSA = 697



Porous structure,
high specific surface
Area (SSA)





Silica is synthesized in a system where both "molecular polymerization" (→ normally called polymerization) and aggregation take place simultaneously (after a short period of plain molecular polymerization in the very beginning)

→ "DUAL POLYMERISATION"

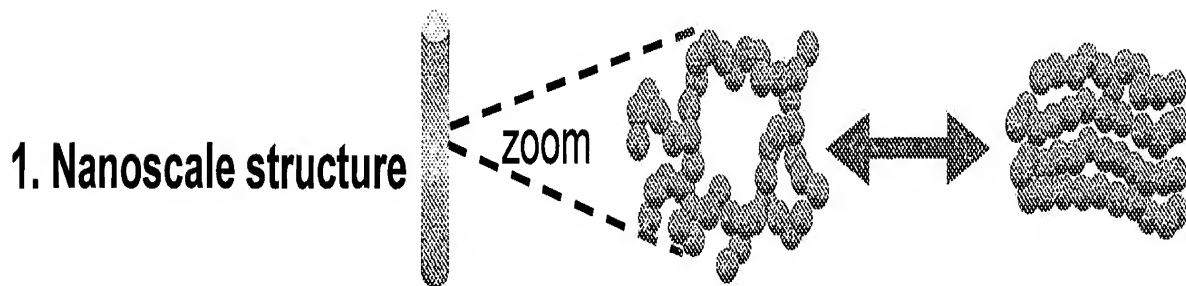
- Molecular polymerization occurs by polycondensation
→ "chemical structure"

Silica polymers (oligomers) tend to form cyclic structures that turn into particles that start to aggregate. In some conditions, like R2 & pH2, silica polymers grow more linearly leaving more Si-OH on the surface

- Aggregation depends on colloidal stability
→ pore structure

Biodegradation rate of silica depends both on the "chemical structure" and nanoscale pore structure

→ i.e. both on molecular polymerization and aggregation



→ aggregation of particles → pore structure

2. Degree of condensation of Si-OH → amount of OH groups

→ polycondensation of Si-OH groups → chemical structure

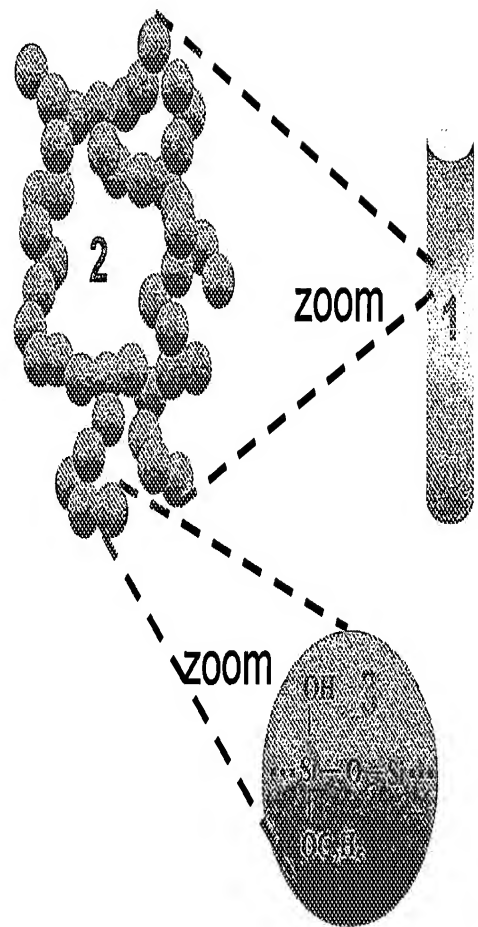
Resulting Silica Structure

3 Levels of Structure

1. Macro- & microscopic level

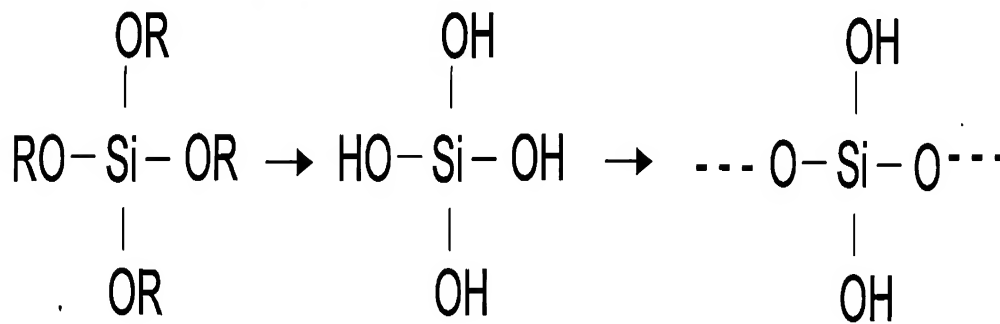
2. Nanoscale: pore structure
- 2-100 nm

3. Molecular level



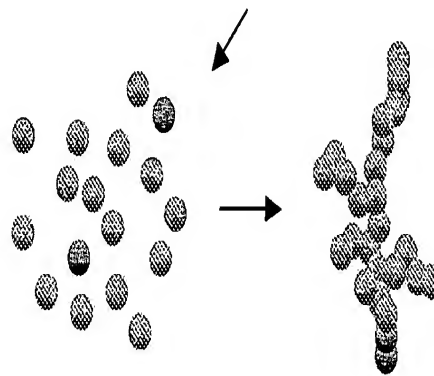
DUAL POLYMERIZATION OF SILICA (or actually "three ways" of polymerization, the third one, aggregation by condensation is difficult to show unambiguously)

1. "Molecular polymerization"; monomer by hydrolysis → condensation

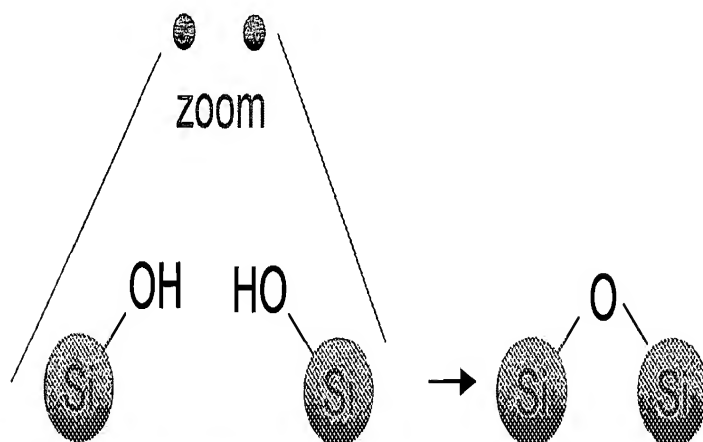


Resulting chem. structure:
Mixture of SiO_2 and SiOH ,
Number of SiOH and length
& form of polymers depend
on precursor ratios and
process parameters

2. Aggregation by coagulation ("particle polymerization"), bonding by Van der Waals forces



Resulting pore structure:
Chem. Structure of particles
originates from molecular
polymerization, pore structure
depends on precursor ratios
and process parameters that
affect the aggregation. Desired
chemical structure can be
"locked" by causing fast
aggregation with subsequent
gel formation



3. "Chemical aggregation", i.e., aggregation by condensation between small particles (does not increase much the degree of condensation, because only one of many SiOH groups in the particle is condensed)